EXECUTIVE ORDER 12866 SUBMISSION

Important

Please read the Instructions on the reverse side before completing this form.

For additional forms or assistance in completing this form, contact the OIRA Docket Library, [202] 395-6880, or your OIRA Desk Officer.

Send three copies of this form and supporting material (four copies if Economically Significant or an Unfunded Mandate) to:

Office of Information and Regulatory Affairs
Office of Management and Budget
Attention: Docket Library, Room 3201
725 17th Street N.W.
Washington, DC 20503

1. Agency/Subagency originating request:
US EPA, Office of Prevention, Pesticides and Toxic Substances (OPPTS)

2. Regulation Identifier Number (RIN):
2070-AD57

3. Title:
Human Testing; Advance Notice of Proposed Rulemaking

4. Stage of Development
__X__ Prerule
_____ Proposed Rule
_____ Interim Final Rule
_____ Final Rule
_____ Final Rule -No material change
_____ Notice
_____ Other

_____
Description of Other

5. Legal Deadline for this Submission:
a) ☐ Yes ■ No
b) Date: _____/_____/_____ (DD MM YY)
c) ☐ Statutory ☐ Judicial

6. Designations
a) Economically Significant (E.O. 12866)
☐ Yes ■ No
b) Unfunded Mandate (2 U.S.C. 1532)
☐ Yes ■ No
If either of the above is "Yes," submit four (4) complete packages to OIRA.

7. Agency Contact (person who can best answer questions regarding the content of this submission):
Angela F. Hofmann, Office of the Assistant Administrator Phone (**202**) **564-0258**

Certification for Executive Order 12866 Submissions
The authorized regulatory contact and the program official certify that the agency has complied with the requirement of E.O. 12866 and any applicable policy directives.

Signature of Program Official:
//s//*Angela F. Hofmann*
Angela F. Hofmann, Director of Regulatory Coordination for OPPTS
Date:
March 12, 2003

Signature of Authorized Regulatory Contact:
//s//*Jane Stewart*
Jane Stewart, Deputy Director of Regulatory Management for EPA
Date:
March 12, 2003

INSTRUCTIONS FOR REQUESTING OMB REVIEW UNDER EXECUTIVE ORDER 12866

GENERAL

Please make sure to answer all questions and have the appropriate officials sign the form.

1. Agency/Subagency

Provide the name of the agency or subagency originating the request. For most Cabinet-level agencies, a subagency designation is also necessary. For non-Cabinet agencies, the subagency designation is generally unnecessary.

EXAMPLE

1. Agency/Subagency originating request:
Department of the Interior
National Park Service
or
Office of Personnel Management

2. Regulation Identifier Number (RIN)

The RIN is the means by which rules are linked across the Unified Agenda of Federal Regulations (Agenda), the Regulatory Plan, and Executive Order 12866.

RINs are assigned to items in the Agenda by the Regulatory Information Service Center (Center). For E.O. 12866 submissions that have not appeared in the Agenda, the agency must obtain a RIN from the Center. The RIN is a prerequisite to the regulatory action being logged in at OIRA.

EXAMPLE

2. Regulation Identifier Number (RIN)
1024-AA12

3. Title

Please provide a brief title that describes, as specifically as you can, the subject of this rulemaking. Avoid using general headings or the title of the CFR part for your rulemaking. To the extent possible, you should keep the title the same as in the Agenda. Also, you should use the same title for all stages of a rulemaking.

4. Stages of Development

Check the stage of development for this action.

Check "Prerule" when the action submitted for review seeks to determine whether or how to initiate rulemaking. Examples include ANPRMs and reviews of existing regulations.

Check "Proposed Rule" when the action submitted will be published in the Proposed Rules section of the Federal Register (for example, an NPRM).

Check "Interim Final Rule" when the action submitted will be published in the Rules and Regulations section of the Federal Register with an Action caption of Interim Rule or Interim Final Rule.

Check "Final Rule" when the action submitted will be published in the Rules and Regulations section of the Federal Register and there have been material changes in the facts and circumstances upon which the previous action was based.

Check "Final Rule - No material change" when the action submitted is associated with a previous request (for example, an NPRM) and there has been no material change in the facts and circumstances upon which the previous action was based.

Check "Notice" when the action submitted will be published in the Notices section of the Federal Register.

Check "Other" when the action does not meet the criteria of any of the above categories. (Indicate on the line provided what type of action you are submitting; for example, a policy statement.)

5. Legal Deadline for This Submission

The deadline is for the regulatory action in this submission only and not for any future or past action in this rulemaking proceeding.

a) Indicate whether the action submitted is subject to any specific legal deadline. For example, if this submissions for an NPRM

and the Final Rule Stage has a deadline, check No. If this submission is for the Final Rule, check Yes.

b) If 5a is Yes, provide the month, day, and year of the deadline for this action (whether past or future).

c) If 5a is Yes, indicate whether the deadline is statutory of judicial.

6. Economically Significant

Check Yes if the action submitted will likely have an annual effect on the economy of $100 million or more or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health and safety, or State, local, or tribal governments or communities. (Section 3(f)(1) of E.O. 12866.)

7. Agency Contact

Provide the name and telephone number of the agency person best able to answer questions regarding the content of this submission.

FILE NAME: HumStudANPR 3-12-03-EO 12866-Submission

DELIBERATIVE — DO NOT CITE OR QUOTE

ENVIRONMENTAL PROTECTION AGENCY

[RIN: 2070-AD57]

[OPP-00XXX; FRL-XXXX-X]

Human Testing; Advance Notice of Proposed Rulemaking

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This notice announces EPA's plan to conduct rulemaking about criteria and standards EPA would apply in deciding the extent to which it will consider or rely on various types of research with human subjects to support its actions. This notice also initiates the rulemaking process by requesting public comments and suggestions on a broad range of issues relating to this subject.

DATES: Comments must be received on or before [*insert date* **[ninety]** *days after date of publication in the* **Federal Register**].

ADDRESSES: Submit your comments, identified by docket ID number OPP-2003-**[insert the docket ID number assigned by your Docket]**, online at http://www.epa.gov/edocket (EPA's preferred method) or mailed to the Public Information and Records Integrity Branch (PIRIB), Office of Pesticide Programs (OPP), Environmental Protection Agency, (7502C), 1200 Pennsylvania Ave., NW, Washington, DC, 20460-0001. For additional submission methods and detailed instructions, go to Unit I.C. of the **SUPPLEMENTARY INFORMATION** section.

FOR FURTHER INFORMATION CONTACT: William L. Jordan, **Mailcode 7501-C**, Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: **703-305-1049** fax number: **703-308-4776;** e-mail address: **jordan.william**@epa.gov.

SUPPLEMENTARY INFORMATION:

This Advance Notice of Proposed Rulemaking (ANPR) is organized into four Units. Unit I contains "General Information" about the applicability of this Notice, how to obtain additional information, how to submit comments in response to the request for comments, and certain other related matters. Unit II provides background and historic information pertaining to human subject research. Unit III describes the rulemaking process, identifies relevant statutory provisions, and requests public comments and suggestions on a broad range of issues related to the Agency's consideration of or reliance on research with human subjects. Unit IV describes procedures followed in the development of this ANPR and certain statutes and Executive Orders that the public may wish to consider in preparing comments.

I. General Information

A. Does this Action Apply to Me?

This action is directed to the public in general. This action may, however, be of particular interest to those who conduct testing of substances regulated by EPA. Since other entities may also be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. *How Can I Get Copies of This Document and Other Related Information?*

1. *Docket.* EPA has established an official public docket for this action under docket identification (ID) number OPP-2003-XXXX. The official public docket consists of the documents specifically referenced in this action, any public comments received, and other information related to this action. Although a part of the official docket, the public docket does not include Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. The official public docket is the collection of materials that is available for public viewing at the Public Information and Records Integrity Branch (PIRIB), Rm. 119, Crystal Mall #2, 1921 Jefferson Davis Hwy., Arlington, VA. This docket facility is open from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The docket telephone number is (703) 305-5805.

2. *Electronic access.* You may access this Federal Register document electronically through the EPA Internet under the "Federal Register" listings at http://www.epa.gov/fedrgstr/. A frequently updated electronic version of 40 CFR part [insert number] is available at http://www.access.gpo.gov/nara/cfr/cfrhtml_00/Title_40/40cfr[insert part number]_00.html, a beta site currently under development.

An electronic version of the public docket is available through EPA's electronic public docket and comment system, EPA Dockets. You may use EPA Dockets at http://www.epa.gov/edocket to submit or view public comments, access the index listing of the contents of the official public docket, and to access those documents in the public docket that are available electronically. Once in the system, select "search," then key in the appropriate docket ID number.

Certain types of information will not be placed in the EPA Dockets. Information claimed as CBI and other information whose disclosure is restricted by statute, which is not included in the official public docket, will not be available for public viewing in EPA's electronic public docket. EPA's policy is that copyrighted material will not be placed in EPA's electronic public docket but will be available only in printed, paper form in the official public docket. To the extent feasible, publicly available docket materials will be made available in EPA's electronic public docket. When a document is selected from the index list in EPA Dockets, the system will identify whether the document is available for viewing in EPA's electronic public docket. Although not all docket materials may be available electronically, you may still access any of the publicly available docket materials through the docket facility identified in Unit I.B.1. EPA intends to work towards providing electronic access to all of the publicly available docket materials through EPA's electronic public docket.

For public commenters, it is important to note that EPA's policy is that public comments, whether submitted electronically or on paper, will be made available for public viewing in EPA's electronic public docket as EPA receives them and without change, unless the comment contains copyrighted material, CBI, or other information whose disclosure is restricted by statute. When EPA identifies a comment containing copyrighted material, EPA will provide a reference to that material in the version of the comment that is placed in EPA's electronic public docket. The entire printed comment, including the copyrighted material, will be available in the public docket. Public comments submitted on computer disks that are mailed or delivered to the docket will be transferred to EPA's electronic public docket. Public comments that are mailed or delivered to the docket will be scanned and placed in EPA's electronic public docket. Where practical, physical objects will be photographed, and the photograph will be placed in EPA's electronic public docket along with a brief description written by the docket staff.

C. *How and To Whom Do I Submit Comments?*

You may submit comments electronically, by mail, or through hand delivery/courier. To ensure proper receipt by EPA, identify the appropriate docket ID number in the subject line on the first page of your comment. Please ensure that your comments are submitted within the specified comment period. Comments received after the close of the comment period will be marked "late." EPA is not required to consider these late comments. If you wish to submit CBI or information that is otherwise protected by statute, please follow the instructions in Unit I.D. Do not use EPA Dockets or e-mail to submit CBI or information protected by statute.

1. *Electronically.* If you submit an electronic comment as prescribed in this unit, EPA recommends that you include your name, mailing address, and an e-mail address or other contact information in the body of your comment. Also include this contact information on the outside of any disk or CD ROM you submit, and in any cover letter accompanying the disk or CD ROM. This ensures that you can be identified as the submitter of the comment and allows EPA to contact you in case EPA cannot read your comment due to technical difficulties or needs further information on the substance of your comment. EPA's policy is that EPA will not edit your comment, and any identifying or contact information provided in the body of a comment will be included as part of the comment that is placed in the official public docket, and made available in EPA's electronic public docket. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment.

i. *EPA Dockets.* Your use of EPA's electronic public docket to submit comments to EPA electronically is EPA's preferred method for receiving comments. Go directly to EPA Dockets at http://www.epa.gov/edocket, and follow the online instructions for submitting comments. Once in the system, select "search," and then key in docket ID number OPP-2003-XXXX. The system is an "anonymous access" system, which means EPA will not know your identity, e-mail address, or other contact information unless you provide it in the body of your comment.

ii. *E-mail.* Comments may be sent by e-mail to opp-docket@epa.gov, Attention: Docket ID Number OPP-2003-XXXX. In contrast to EPA's electronic public docket, EPA's e-mail system is not an "anonymous access" system. If you send an e-mail comment directly to the docket without going through EPA's electronic public docket, EPA's e-mail system automatically captures your e-mail address. E-mail addresses that are automatically captured by EPA's e-mail system are included as part of the comment that is placed in the official public docket, and made available in EPA's electronic public docket.

iii. *Disk or CD ROM.* You may submit comments on a disk or CD ROM that you mail to the mailing address identified in Unit I.C.2. These electronic submissions will be accepted in WordPerfect or ASCII file format. Avoid the use of special characters and any form of encryption.

2. *By mail.* Send your comments to: Public Information and Records Integrity Branch (PIRIB), Office of Pesticide Programs (OPP), Environmental Protection Agency (7502C), 1200 Pennsylvania Ave., NW., Washington, DC, 20460-0001, Attention: Docket ID Number OPP-2003-XXXX.

3. *By hand delivery or courier.* Deliver your comments to: Public Information and Records Integrity Branch (PIRIB), Office of Pesticide Programs (OPP), Environmental Protection Agency, Rm. 119, Crystal Mall #2, 1921 Jefferson Davis Hwy., Arlington, VA., Attention: Docket ID Number OPP-2003-XXXX. Such deliveries are only accepted during the docket's normal hours of operation as identified in Unit I.A.1.

D. *How Should I Submit CBI To the Agency?*

Do not submit information that you consider to be CBI electronically through EPA's electronic public docket or by e-mail. You may claim information that you submit to EPA as CBI by marking any part or all of that information as CBI (if you submit CBI on disk or CD ROM, mark the outside of the disk or CD ROM as CBI and then identify electronically within the disk or CD ROM the specific information that is CBI). Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

In addition to one complete version of the comment that includes any information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket and EPA's electronic public docket. If you submit the copy that does not contain CBI on disk or CD ROM, mark the outside of the disk or CD ROM clearly that it does not contain CBI. Information not marked as CBI will be included in the public docket and EPA's electronic public docket without prior notice. If you have any questions about CBI or the procedures for claiming CBI, please consult the person listed under FOR FURTHER INFORMATION CONTACT."

E. What Should I Consider as I Prepare My Comments for EPA?

You may find the following suggestions helpful for preparing your comments:

1. Explain your views as clearly as possible.
2. Describe any assumptions that you used.
3. Provide copies of any technical information and/or data you used that support your views.
4. If you estimate potential burden or costs, explain how you arrived at the estimate that you provide.
5. Provide specific examples to illustrate your concerns.
6. Offer alternative ways to improve the notice or collection activity.
7. Make sure to submit your comments by the deadline in this notice.
8. To ensure proper receipt by EPA, be sure to identify the docket control number assigned to this action in the subject line on the first page of your response. You may also provide the name, date, and Federal Register citation.

II. Introduction

A. Background on Standards for Conducting Human Research

Over the years, scientific research with human subjects has provided much valuable information to help characterize and control risks to public health, but its use has also raised particular ethical concerns for the welfare of the human participants in such research as well as scientific issues related to the role of such research in assessing risks. Society has responded to these concerns by defining general standards for conducting human research. In the United States, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued in 1979 The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. This document can be found on the web at http://ohsr.od.nih.gov/mpa/belmont.php3.

For most federal agencies in the United States, the principles of the Belmont Report are implemented through the Common Rule, which was developed cooperatively by some 17 departments and agencies, including EPA, and which guides all research with human subjects conducted or supported by these departments and agencies of the federal government. The Common Rule as promulgated by EPA (40 CFR Part 26) has guided human research conducted or supported by EPA since it was put in place in 1991.

More broadly, the international medical research community has developed and maintains ethical standards documented in the Declaration of Helsinki, first issued by the World Medical Association in 1964 and revised several times since then. These standards apply to diagnostic and therapeutic medical research, and to research that adds to understanding of the causes of disease and the biological mechanisms that explain the relationships between human exposures to environmental agents and disease.

In addition, many public and private research and academic institutions and private companies, both in the United States and in other countries, including non-federal U.S. and non-U.S. governmental organizations, have their own specific policies related to the protection of human participants in research.

Much of the scientific research supporting EPA's actions, including a significant portion of the research with human subjects submitted to the Agency or retrieved by the Agency from published sources, is conducted by this broader research community, without direct participation or support by the U.S. government. Such research, referred to here as "third party" research, while it may be governed by specific institutional policies intended to protect research participants or may fall within the scope of the Declaration of Helsinki, is not subject to the Common Rule. In general, EPA can not readily determine whether such policies are consistent with or as protective of human subjects as the Common Rule, nor the extent to which such policies or standards have been followed in the conduct of any particular study. Thus even well-conducted third-party human studies may raise difficult questions for the Agency when it seeks to determine their acceptability for consideration.

B. Human Research Issues in EPA's Pesticide Program

Questions about the Agency's consideration of and reliance on third-party human research studies have arisen most notably, but not exclusively, in EPA's pesticides program. Under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), EPA may require

pesticide companies to conduct studies with human subjects, for example, to measure potential exposure to pesticide users or to workers and others who re-enter areas treated with pesticides, and to evaluate the effectiveness of pesticide products intended to repel insects and other pests from human skin. In addition, EPA sometimes encourages other research with human subjects, including tests of the potential for some pesticides–generally those designed for prolonged contact with human skin–to irritate or sensitize human skin, and tests of the metabolic fate of pesticides in the human system. These latter studies typically precede monitoring studies of agricultural workers and others to protect them from exposure to potentially dangerous levels of pesticide residues.

In addition to these kinds of research which have been required or encouraged by EPA, other kinds of human studies with pesticides have occasionally been submitted to the agency voluntarily. Among these voluntarily submitted studies have been tests involving intentional dosing of human subjects to establish a No Observed Adverse Effect Level (NOAEL) or No Observed Effect Level (NOEL) for systemic toxicity of certain pesticides to humans. Before passage of the Food Quality Protection Act in 1996, submission of such studies was rare. EPA considered and relied on human NOAEL/NOEL studies in a few regulatory decisions on pesticides made prior to 1996. Since the passage of FQPA, submission of these types of studies to the Office of Pesticide Programs has increased; the Agency has received some twenty studies of this kind since 1996.

In response to concerns about human testing expressed in a report of a non-governmental advocacy organization, the Environmental Working Group, in July, 1998, the Agency began a systematic review of its policy and practice. In a press statement on July 28, 1998, EPA noted that it had not relied on any such studies in any final decisions made under FQPA; this remains true today.

In further response to growing public concern over pesticide research with human subjects, EPA convened an advisory committee under the joint auspices of the EPA Scientific Advisory Board (SAB) and the FIFRA Scientific Advisory Panel (SAP) to address issues of the scientific and ethical acceptability of such research. This advisory committee, known as the Data from Testing of Human Subjects Subcommittee (DTHSS), met in December 1998 and November 1999, and completed its report in September, 2000. Their report is available in the Docket cited above in this notice, and on the web at: http://www.epa.gov/science1/pdf/ec0017.pdf

The DTHSS advisory committee heard many comments at their two public meetings, and further comments have been submitted in response to their published report. No clear consensus
emerged from the advisory committee process on the acceptability of NOAEL or NOEL studies of systemic toxicity of pesticides to human subjects, and significant differences of opinion remain on both their scientific merit and ethical acceptability. A vigorous public debate continues about the extent to which EPA should accept, consider, or rely on third-party intentional dosing human toxicity studies with pesticides.

C. EPA's Current Agency-wide Focus on Human Research Issues

EPA is now interested in addressing these issues more broadly, and in all Agency programs. In December, 2001, EPA asked the advice of the National Academy of Sciences (NAS) on the many difficult scientific and ethical issues raised by this debate, and also stated the

Agency's interim approach on third-party intentional dosing human subjects studies.[1] At that time the Agency committed that when it receives the NAS report, "EPA will engage in an open and participatory process involving federal partners, interested parties and the public during its policy development and/or rule making regarding future acceptance, consideration or regulatory reliance on such human studies." Since making that commitment, EPA has decided to initiate a rulemaking process by issuing this notice.

Under a contract with EPA, the NAS has convened a committee to provide the requested advice. The committee met in December 2002, and again in January and March 2003. The membership, meeting schedule, and other information about the work of this committee can be found on the NAS website at:

http://www4.nas.edu/webcr.nsf/5c50571a75df494485256a95007a091e/9303f725c15902f685256c44005d8931?OpenDocument&Highlight=0,EPA.

The committee's final report is due in December 2003.

Notwithstanding these many recent developments concerning human studies, some things have not changed. EPA remains committed to full compliance with the Common Rule for all research with human subjects conducted or supported by the Agency. The Agency is proud of its record in this regard, and proud of the scientific quality of the research performed in its own laboratories and with various partners. This body of research has provided many important insights and has contributed significantly to the protection of human health. The Agency will continue to conduct and support such research, and to consider and rely on its results in Agency actions. EPA also remains committed to scientifically sound assessments of the hazards of environmental agents, taking into consideration available, relevant, and appropriate scientific research.

III. EPA's Rulemaking Process and Request for Public Comment

EPA intends to undertake notice-and-comment rulemaking on the subject of its consideration of or reliance on research involving human subjects. The Agency will particularly focus on third-party intentional dosing human studies, but recognizes that the principles applicable to third-party studies may also be relevant to studies conducted or supported by the government. The first step in this process is this advance notice of proposed rulemaking which calls for comments and suggestions from all interested parties. The next step the Agency would expect to

[1] The Agency's press release on this subject is on the web at http://yosemite.epa.gov/opa/admpress.nsf/b1ab9f485b098972852562e7004dc686/c232a45f5473717085256b2200740ad4?OpenDocument

In early 2002 various parties from the pesticide industry filed a petition with the U. S. Court of Appeals for the District of Columbia for review of EPA's December 2001press release. These parties argued that the Agency's interim approach constituted a "rule" promulgated in violation of the procedural requirements of the Administrative Procedure Act and the Federal Food, Drug, and Cosmetic Act. The court has denied motions concerning emergency relief and other matters, briefs have been filed, and oral argument of the merits of the case is scheduled for March 2003.

undertake would be to issue a proposed rule for public comment. In developing any proposed rule EPA will consider the advice in the National Academy of Sciences committee report, along with comments received in response to this notice. Comments received on any proposed rule would then be taken into consideration in developing a final rule or policy.

In general, the Agency expects that any rule or policy coming out of this process may do one or more of the following:

- Specify, if and to the extent determined by EPA to be appropriate, that EPA would not accept, consider, or rely on results from particular types of studies involving intentional dosing of human subjects or from human studies with particular characteristics;

- Establish minimum standards relating to the protection of human subjects which would be required to be met in the design and conduct of a study with human subjects not otherwise precluded from consideration, in order for EPA to accept, consider, or rely on the results of the study;

- Establish procedures for ensuring that any minimum standards for the conduct of third-party research with human subjects had been adhered to in the conduct of any such study that EPA intended to accept, consider, or rely on.

A. Legal Authority

Section 25(a) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) gives the Administrator authority to "prescribe regulations to carry out the purposes of [FIFRA]." Such a rule would implement EPA's authority to require data in support of registration of pesticides (see, for example, FIFRA sections 3(c)(1)(F) and 3(c)(2)(B)) and to interpret the provision making it unlawful for any person "to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test." (FIFRA sec. 12(a)(2)(P)). In addition, section 408(e)(1)(C) of the Federal Food, Drug and Cosmetic Act (FFDCA) authorizes the Administrator to issue a regulation establishing "general procedures and requirements to implement this section."

The Clean Air Act gives EPA general rulemaking authority in 42 U.S. C. 7601(a). The Clean Water Act, 33 U.S.C. sec. 1361, authorizes the Administrator to promulgate regulations necessary to carry out the Agency's functions under that Act. Section 42 U.S. C. 9615 in the Comprehensive Environmental Response, Compensation, and Liability Act authorizes the President to establish regulations to implement the statute; this authority has been delegated to EPA by Executive Order 12580. The Emergency Planning and Community Right-to-Know Act also contains a general rulemaking provision, 42 U.S.C. 11048, authorizing the Administrator to promulgate rules necessary to carry out the Act. The Resource Conservation and Recovery Act specifically authorizes the Administrator to prescribe regulations necessary to carry out EPA's functions under the Act, 42 U.S.C. 6912. The Safe Drinking Water Act contains similar language, authorizing the Administrator to prescribe such regulations "as are necessary and appropriate" to carry out EPA's functions under the Act, 42 U.S.C. 300j-9. In addition, EPA has authority under 5 U.S.C. 301 and 42 U.S.C. 300v-1(b).

B. Request for Comments

Neither this notice nor the specific questions presented below for public comment are intended to indicate that EPA now favors any particular policy approaches regarding the Agency's consideration of or reliance on third-party intentional dosing human studies. Similarly, neither this notice nor the specific questions presented below for public comment are intended to indicate that EPA has decided on a particular scope for any potential future rulemaking. Nor is this notice intended to impede or otherwise delay any Agency assessments or actions. Rather, this notice is designed to encourage public input from all interested parties on a broad range of issues that could help inform any rule or policy that EPA eventually promulgates or issues, respectively.

The Agency fully appreciates the number, the range, and the interconnectedness of the scientific and ethical concerns raised especially by intentional dosing human studies of the wide range of environmental agents addressed by EPA's programs. Reflecting the breadth of issues that have been raised in the course of the public debate to this point, the Agency has identified a number of specific questions on which it particularly invites comment. These questions are intended to help organize and focus the discussion, but not to constrain it. Commenters should feel free to address any other relevant topics as well.

4. Applicability of Existing Standards

a. Is it appropriate to use a standard intended to guide the conduct of research, (e.g., the Common Rule, Declaration of Helsinki, or the Nuremberg Code) to assess the acceptability for review of completed research?

b. Is it appropriate to use a standard intended to guide the conduct of therapeutic or diagnostic medical research or to clarify causes of disease, such as the Declaration of Helsinki, to assess the acceptability for review of other kinds of research without diagnostic or therapeutic intent, conducted with healthy subjects?

c. Should the Agency apply a different standard of acceptability depending on the type of substance tested (e.g., pharmaceutical, pesticide, pathogen, or environmental contaminant)? If so, how might the differing standards be applied when a single substance has multiple uses, e.g., as both a pesticide and a drug?

d. Does it matter who maintains a standard, or by what process it is maintained? For example, would it be appropriate for EPA to accept and apply a standard maintained by a private, non-governmental organization, and subject to change without public notice and comment or U.S. Government endorsement, as is the Declaration of Helsinki?

e. Should the Agency extend the requirements of the Common Rule to the conduct of third-party research with human subjects intended for submission to EPA? What are the advantages and disadvantages of conducting a rulemaking for this purpose alone, as opposed to one with a broader scope?

5. Should the standard of acceptability vary depending on the research design?

a. Should the Agency apply a different standard of acceptability depending on whether the research design involves intentional exposure? For example, should the same standard apply to research involving intentional exposures to human subjects, to research designed to follow-up accidental exposure, and to studies of individuals

occupationally or incidentally exposed?

b. Should the Agency apply a different standard of acceptability depending on the level of exposure of the human subjects? For example, when research involves intentional exposure to a pesticide, does it matter if exposure results from use of the pesticide in conformity with approved label directions, or if the level of exposure is below the Reference Dose or other established health standard designed to protect the general public?

c. Should the Agency apply a different standard of acceptability depending on the pathway of exposure? For example, should the same standard apply when exposure is oral, or dermal, or by inhalation?

d. Should the Agency apply a different standard of acceptability depending on the effects being evaluated? For example, should the same standard apply to a study of localized skin irritation or dermal sensitization that applies to a study of systemic dermal toxicity? Should the same standard apply to a study measuring transitory changes in blood chemistry or levels of a substance in urine that applies to studies measuring longer-lasting changes? Should the same standard apply to studies measuring organoleptic effects, such as taste or smell, that applies to studies of toxic effects? Should the same standard apply to measurements of toxic effects and to measurements through genomic or proteomic assessments?

e. Should conduct of research in compliance with the provisions of the Common Rule or another standard for the protection of human subjects be accepted as evidence of its ethical acceptability?

f. Should the Agency apply a different standard of acceptability to research which is performed consistent with an EPA guideline for data development? For example, EPA has published guidelines for certain kinds of human studies currently required for pesticide registration; should conduct of a required study in full compliance with an EPA guideline be accepted as evidence of its acceptability?

g. Should the Agency apply a different standard of acceptability depending on a study's statistical power?

h. Should the Agency apply a different standard of acceptability depending on whether a human study design is able to measure the same endpoints in humans that have been observed in animal testing of the same substance?

i. Should the Agency apply a different standard of acceptability to intentional dosing studies depending on whether there are alternative methods of obtaining data of comparable scientific merit that would not require deliberate exposure of humans?

j. Should the Agency apply a different standard of acceptability to studies involving children as test subjects?

3. Should the standard of acceptability vary depending on the provenance of the research?

a. Should the Agency apply a different standard of acceptability depending on who or what organization sponsors or supports the research? Since 1991, human research conducted or supported by the US government has been subject to the Common Rule. Should the same standard apply to research conducted or supported by others? Should standards differ when the sponsor is a commercial enterprise, or a non-profit organization, another government in the United States (such as state, tribal, or local), or the government in another country? Should the standard differ depending on the test sponsor's interest in a regulatory matter that could be affected by EPA's consideration of the data?

b. Should the Agency apply a different standard of acceptability depending on who or what organization conducts the research? For example, a research organization–public or private–holding a "Federal-Wide Assurance" from the Department of Health and Human Services's Office of Human Research Protections usually promises to comply with the Common Rule in all its human research, without regard to the identity of the sponsor or supporter of the research. Should third-party work conducted by a research organization holding a Federal-Wide Assurance be assessed by a different standard than other third-party human research?

c. Should the Agency apply a different standard of acceptability depending on where the research was conducted? For example, does it matter whether research is conducted entirely in the United States or partially in the United States? If it is conducted outside the United States, does it matter in what country it is conducted? What are the advantages and disadvantages of judging the acceptability of human studies based on a single uniform standard versus prevailing local standards (e.g., in different countries)?

d. Should the Agency apply a different standard of acceptability depending on the reasons the research was conducted?

e. Should the Agency apply a different standard of acceptability to submitted research depending on who submitted it? For example, should the same standard apply to submissions from regulated industry, from public interest groups, from the public, or from other governments? Should the Agency apply a different standard of acceptability depending on whether the study was submitted voluntarily, or in response to a particular regulatory requirement of EPA?

f. Should the Agency apply a different standard of acceptability to human research which is not submitted, but which the Agency obtains at its own initiative from the scientific literature or other sources, depending on how or where EPA obtains it?

4. *Should the standard of acceptability vary depending on EPA's potential use of the data?*

a. Should the Agency apply a different standard of acceptability depending on whether the results of the study would support a more or less stringent regulatory position? For example, should the same standard apply whether the data indicate that the substance tested is more risky or less risky than is indicated by other available data?

b. Should the Agency apply a different standard of acceptability depending on how EPA intends to use the results–e.g., to reduce or remove the usual tenfold interspecies uncertainty factor, to provide an endpoint for use in calculating a Reference Dose or Reference Concentration for the test substance, to provide a dose-response function for use in quantitative risk assessment, or for some other purpose?

5. *Should the standard of acceptability vary depending on EPA's assessment of the benefits of the research to the subjects or to society?*

a. Should the Agency independently consider the benefits of the research to the research subjects or to society, or should it defer to the judgment of Institutional Review Boards or similar oversight panels?

b. If EPA were to assess independently the benefits of research to the research subjects or to society, on what range of information should it base its assessment? How might EPA obtain information relevant to such an assessment?

6. *How should the Agency implement standards of acceptability?*

a. To what extent and how should the submitter of research with human subjects to EPA be required to document or otherwise demonstrate compliance with appropriate standards for the protection of human research subjects—e.g., fully informed and fully voluntary participation, and independent oversight of research design and conduct by an Institutional Review Board or comparable entity?

b. How should the Agency determine compliance with an appropriate standard for human research data which is not submitted, but which it obtains from the scientific literature or other sources?

c. To what extent should new standards be applied to research which has already been conducted, or is underway? Does fairness require a period of transition to any new rule or standards of acceptability, or do other considerations override that factor?

d. Should the Agency apply a different standard of acceptability to research already submitted to or obtained by EPA and to research newly submitted to or obtained by EPA? Should previous submitters be allowed time to submit supplemental information to demonstrate compliance with any new standards of acceptability?

e. Is rulemaking needed at all? Would it be better to address the issues surrounding acceptance of human research, or some of them, by other means, such as policy statements or internal guidelines?

IV. Statutory and Executive Order Reviews

Under Executive Order 12866, entitled *Regulatory Planning and Review* (58 FR 51735, October 4, 1993), it has been determined that this advance notice of proposed rulemaking is a "significant regulatory action" under section 3(f) of the Executive Order. The Agency therefore submitted this document to OMB for the 10-day review period afforded under this Executive Order. Any changes made in response to OMB comments during that review have been documented in the public docket as required by the Executive Order.

Since this advance notice of proposed rulemaking does not impose any requirements, and instead seeks comments and suggestions for the Agency to consider in developing a subsequent notice of proposed rulemaking, the various other review requirements that apply when an agency imposes requirements do not apply to this action.

As part of your comments on this advance notice of proposed rulemaking you may include any comments or information that you have regarding these requirements. In particular, any comments or information that would help the Agency to assess the potential impact of a rule on small entities pursuant to the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 et seq.); to consider voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act of 1995 (NTTAA), Public Law 104-113, section 12(d) (15 U.S.C. 272 note); or to consider environmental health or safety effects on children pursuant to Executive Order 13045, entitled Protection of Children from Environmental Health Risks and Safety Risks (62 FR 19885, April 23, 1997). The Agency will consider such comments during the development of any subsequent notice of proposed rulemaking as it takes appropriate steps to address any applicable requirements."

List of Subjects

Environmental protection, protection of human research subjects

Dated:_____

_____

Administrator

[FR Doc. 01-?????? Filed ??-??-01; 8:45 am]

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